World Bank Training Program on HIV/AIDS Drugs

Training Module 3
Selection and Quantification

based on the World Bank document

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Module Learning Objectives

• The learner will be able to initiate a rational selection of HIV/AIDS care package (also: Anti Retroviral Treatment Supplies: ARTS)

• The learner will be able to quantify ARTS

• The learner will be able to adapt selection and quantification processes to rapidly changing contexts

Pages 31-50, Chap. 4: Battling HIV/AIDS
Outline Unit 1
Treatment

• Therapeutic & clinical goals in HIV/AIDS treatment
• Treatment of HIV infections in various population groups
• WHO Clinical Staging for adults and adolescents, when to start treatment
• Treatment of Opportunistic Infections (OI)
Outline Unit 2
Product Selection

• Basic elements of the selection process
• Selection of ARVs based on treatment protocols
• Public health considerations of 1st line regimens
• Major problems of 2nd line regimens
• WHO recommended 1st & 2nd line regimens for adults and adolescents
• WHO recommended 1st & 2nd line regimens for children
• Simplified guidelines
• Dosages of ARVs for Adults and adolescents
• Non ARV essential commodities
Outline Unit 3
Product Quantification

• What is product quantification
  – key principles of quantification
• Different quantification methods
  – consumption method
  – adjusted consumption method
  – patient morbidity standard
  – treatment method
Unit 1
Treatment

Impact on Sub-Saharan Africa: In 2008, 26.6 million people are HIV positive and there are more than eleven million AIDS orphans. In addition, an estimated five to six million individuals in developing countries are in need of antiretroviral therapy today.

The world community recognizes that HIV/AIDS is a global priority and halting and reversing its spread is one of the Millennium Development Goals. The World Bank and other international organizations, such as the Global Fund for AIDS, Tuberculosis and Malaria, have provided over U.S.
Clinical goals

1. Which treatment is optimal for which group of patients and when to start

Therapeutic goals

2. Which products are needed for those treatments

Post-exposure prophylaxis

Pregnant women

H. workers/Rape victims

Adults/adolescents

Special groups treatment

Opportunistic infections

First line treatment

Second line treatment

3. How much of the selected product

Usage method

Morbidity method

Adjusted usage method
1.1 Therapeutic & Clinical Goals in HIV/AIDS Treatment

- Improved quality of life—with effects for the individual, family, and society.
- Restoration or preservation of immunological functions, enabling people to defend themselves against new infections and recover more quickly from illness.

Maximum and durable suppression of viral replication—within HIV viral RNA detectable limits for the person’s lifetime.
Six Therapeutic Goals in HIV/AIDS Treatment

1. Reduction of HIV related morbidity and mortality
2. Improved quality of life with effects for the individual, the family and the society
3. Restoration and preservation of immunology functions
4. Maximal and durable suppression of viral replication
5. Reduced need for medical intervention and support
6. Prevention/reduction of drug resistant strains of HIV and OI’s
Clinical Goals

- Improved overall health status
- Viral load reduced to <20c/ml, CD4 within normal range
- Reduction and control of drug side effects and support for adherence
Pre-Conditions for Treatment

- Adequate social support and patient care taker available
- Adequate food supplies
- Adequate health facilities nearby
- Appropriate education for the patient re: adherence and side effect issues
- Adequate testing and monitoring available
Basic Components of HIV/AIDS Treatment

• Use of Antiretrovirals to prevent replication of the Human Immunodeficiency Virus (HIV) in cells
• Treatment of Opportunistic Infections caused by a weakened immune system
• Monitoring, evaluation and adjustment of treatment to prevent drug resistance; to maximize effects of ART and to minimize consequences of toxicity and side effects.
1.2 Treatment of HIV Infections in Various Population Groups

- Adults and adolescents
- Pregnant women or women of child-bearing age
- Children
- People with TB & HIV Co-infection
- Health and emergency workers after occupational exposure
- Victims of sexual assault
Treatment of Adults and Adolescents

• First line combination therapy of three ARV’s
• Second line combination therapy
• Customized treatment for patients who cannot tolerate the first and second line regimes
Treatment of Women (pregnant/child-bearing women)

• Aimed at:
  – reducing viral load and disease progression in the mother
  – reducing the risk of toxicity to the fetus
  – preventing the transmission of infection to the neonate

• A separate treatment protocol needs to be agreed upon
Prevention of Mother-To-Child Transmission (PMTCT)

• During Pregnancy
  – ARV mono-therapy or combination therapy

• Birth
  – Cesarean section

• Breastfeeding
  – Avoid breastfeeding if appropriate alternatives are available: in term of HIV transmission, exclusive artificial feeding > exclusive breastfeeding > mixte feeding
Treatment of Children and Infants

- Similar regimes as for adults
- Pediatric dosage is problematic
- Monitoring of children under 6 yrs different
Other special Groups of Patients

- People who have been exposed to HIV contaminated materials or fluids due to occupational hazards, i.e., healthcare workers)
- Victims of sexual assault by HIV infected people
- People with TB and HIV co-infection
1.3 WHO Clinical Stages for adults and adolescents

- **WHO Clinical Stage I (Asymptomatic)**
  - HIV positive, no weight loss
  - No symptoms or only generalized lymphadenopathy
  - Able to do normal activities

- **WHO Clinical Stage II (Mild disease)**
  - Mild weight loss (5-10%), minor disease symptoms: sores or cracks around lips, itching rash, H. Zoster, recurrent upper RI, sinusitis, recurrent mouth ulcers
  - Still able to do normal activities
WHO Clinical Stages for adults and adolescents (Cont'd)

- **WHO Clinical Stage III (Moderate disease)**
  - Weight loss >10%, oral thrush (oral leukoplakia), over 1 month diarrhea or fever, pulmonary TB, severe bacterial infections (pneumonia, muscle infection), TB lymphadenopathy, acute necrotizing ulcerative gingivitis/periodontitis, other bacterial infections
  - May be bedridden <50% per day over a one month period

- **WHO Clinical Stage IV (Severe disease: AIDS)**
  - Bedridden >50% /day over one month period
When to Start ARV in Adults/Adolescents

- **If CD4 testing available:**
  - WHO stage IV disease, *regardless* of CD4 counts
  - WHO stage III disease, *consider ART* using CD4 cell counts <350/mm³ to assist decision-making
  - WHO stage I or II if CD4 cell counts ≤ 200/mm³

* In this situation, the decision to start or defer ARV treatment should take into consideration not only the CD4 cell count and its evolution, but also concomitant clinical conditions

- **If CD4 testing not available***:
  - WHO stages IV & III disease, *regardless* of total lymphocyte count (TLC)
  - WHO stage II disease *with TLC* ≤ 1200/mm³

* TLC = total lymphocyte count; only useful in symptomatic patients; in absence of CD4 testing, would *not* treat stage I asymptomatic adult
1.4 Treatment of Opportunistic Infections (OI)

- Treat promptly in accordance with national protocols, even when ARV’s are not available
- National protocols for the management of OIs required
- Uninterrupted supply of Medicines for key OIs required
Conclusion of Unit 1

The previous slides have shown the potential complexity of ART guidelines and the differences between the various target groups.

Now the selection process can be described.
Unit 2
Product Selection
2.1 Basic Elements of the Selection Process

- Selection committee is multi-disciplinary
  - representatives of AIDS council, national drug formulary committee, HIV specialists (doctors, nurses pharmacists, procurement specialists) & PLWHA

- Drug selection should be based on pre-determined criteria

- Fixed dose combination should be considered to optimize adherence

- Important to use INNs (int'l nonproprietary names instead of brand names)
2.2 Selection of ARV’s Based on National Treatment Protocols

- First line ARV treatment
- Second line ARV treatment
- PMTCT
- Post Exposure prophylaxis
2.3 Considerations that Informed the Choice of First-Line ARV Regimens

- Potency
- Side effect profile
- Maintenance of future options
- Predicted adherence
- Availability of fixed dose combinations of antiretrovirals
- Coexistent medical conditions (TB, and pregnancy or risk thereof)
- Concomitant medications
- Presence of resistant viral strain
- Cost and availability
- Limited infrastructure
- Rural delivery
2.4 Problems with second-line ARV regimens

- Multiple resistance mutations
- High pill burden
- Limited experience
- TDF availability
- ABC hypersensitivity
- Cold chain for RTV
- High cost
### 2.5 WHO Recommended First and Second-Line ARV Regimens for HIV Treatment in Adults/Adolescents

<table>
<thead>
<tr>
<th>First-Line Regimen</th>
<th>Second-Line Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T or ZDV</td>
<td>TDF or ABC</td>
</tr>
<tr>
<td></td>
<td>Plus</td>
</tr>
<tr>
<td>3TC</td>
<td>Plus</td>
</tr>
<tr>
<td></td>
<td>ddI</td>
</tr>
<tr>
<td></td>
<td>Plus</td>
</tr>
<tr>
<td>NVP or EFZ</td>
<td>Protease inhibitor:</td>
</tr>
<tr>
<td></td>
<td>LPV/r or SQV/r *</td>
</tr>
</tbody>
</table>

* NFV in places without cold chain key
### 2.6 WHO Recommended First and Second-Line ARV Regimens for Treatment in Children

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>d4T or ZDV</td>
<td>ABC *</td>
</tr>
<tr>
<td>Plus</td>
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<td>ddI</td>
</tr>
<tr>
<td>Plus</td>
<td>Plus</td>
</tr>
<tr>
<td>NVP or EFZ</td>
<td>Protease inhibitor:</td>
</tr>
<tr>
<td></td>
<td>LPV/r or NFV,</td>
</tr>
<tr>
<td></td>
<td>or SQV/r if wt ≥ 25 kg</td>
</tr>
</tbody>
</table>

* Insufficient PK data on TDF in children to recommend it as alternative NRTI, and concerns re: bone toxicity of TDF
2.7 SIMPLIFIED GUIDELINES FOR ARV TREATMENT (HIV-1 INFECTION)

1st Line Regimen
ZDV/3TC + EFV

If severe anemia
Substitute ZDV to d4T

If severe anemia and neuropathy or pancreatitis
Substitute ZDV to ddI (or ABC)

Therapeutic Failure

2nd Line Regimen
TDF + ddI + LPV/r

If severe CNS symptoms or pregnancy
Substitute EFV to NVP

If hepatitis or severe rash
Substitute EFV to NFV

If severe anemia
Substitute ZDV to ddI (or ABC)

If severe anemia and neuropathy or pancreatitis
Substitute ZDV to ddI (or ABC)

If renal failure
Substitute TDF to ABC

If severe dislipidemia
Substitute LPV/r to NFV (or ATV/r)

If severe GI intolerance
Substitute ddI to ABC

TB/HIV
Substitute LPV/r to SQV/r

key

DISTRICT/REGIONAL LEVEL

LOCAL LEVEL
**Alternative regimens (not in any order of preference)**

<table>
<thead>
<tr>
<th><strong>Women</strong></th>
<th><strong>Infants</strong></th>
<th><strong>Single-dose NVP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV starting at 28 weeks or as soon as feasible thereafter; continue in labour</td>
<td>ZDV for one week</td>
<td></td>
</tr>
<tr>
<td>ZDV + 3TC starting at 36 weeks or as soon as feasible thereafter; continue in labour and for one week postpartum</td>
<td>ZDV + 3TC for one week</td>
<td></td>
</tr>
</tbody>
</table>

**key**
HIV-infected pregnant women with indications for ARV treatment

**Women**
- Follow the treatment guidelines as for non-pregnant adults except that EFV should not be given in the first trimester
- First-line regimens:
  - ZDV + 3TC + NVP or
  - d4T + 3TC + NVP
- Consider delaying initiating ARV treatment until after the first trimester, although for severely ill women the benefits of initiating treatment early clearly outweigh the potential risks

**Infants**
- ZDV for one week or
- single-dose NVP or
- single-dose NVP plus ZDV for one week
What did we know and when did we know it?

1994

U.S. AZT Trial ACTG 076: 14-28 WK
• 67% reduction in transmission

1994

Thai Bangkok short AP/IP AZT trial: 32 wks
• 50% reduction in transmission

1998

Cote d'Ivoire short AP/IP AZT trials
• 37% reduction in transmission (breastfeeding)

1999

PETRA AZT/3TC trial (6 wk results)
• 50% reduction with longest arm.
• 38% reduction with the IP/PP arm

1999

Uganda 2-dose IP/PP NVP trial (HIVNET 012)
• 47% reduction in transmission (breastfeeding: BF)

1999

Thailand Long vs short AZT regimens
• 4% Transmission rate (TR) in LL (non breastfeeding)

2000

DITRAME + 1201.1
• 6.2% TR with AZT & IP/PP NVP (BF)

2002

DITRAME +
• 4.7% TR with AZT/3TC & IP/PP NVP (BF)

2003

Thailand PHPT
• 1.9% TR with AZT + NVP (non BF)

2004

Thailand
• 1.9% TR with AZT + NVP (non BF)
Post-exposure prophylaxis (PEP)

- Start PEP as soon as possible after exposure to HIV (within 72 H) for a duration of 28 days (4 weeks).
- Most commonly used for PEP:
  - Bitherapy: AZT + 3 TC (Zidovudine, Lamivudine) (combivir)
  - 300mg AZT+150mg 3TC twice per day for 28 days
  - Triple combination: AZT + 3 TC + IDV
  - Twice per day Combivir and 3 times IDV 800mg per day
  - or other PI such as NFV, LPV/r

- If drug resistant HIV strain is suspected referral to a specialist is necessary

- Consider also psychological support, prevention of STIs & unwanted pregnancy

  - Clinical Management of Rape Survivors, WHO & UNHCR, 2004: Revised Edition
# 2.8 Dosages of Antiretroviral Drugs for Adults and Adolescents

<table>
<thead>
<tr>
<th>Drug class/drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside RTIs</strong></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>300 mg twice daily</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>400 mg once daily</td>
</tr>
<tr>
<td></td>
<td>(250 mg once daily if &lt;60 kg)</td>
</tr>
<tr>
<td></td>
<td>(250 mg once daily if administered with TDF)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>150 mg twice daily or 300 mg once daily</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>40 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>(30 mg twice daily if &lt;60 kg)</td>
</tr>
<tr>
<td>Zidovudine (ZDV)</td>
<td>300 mg twice daily</td>
</tr>
<tr>
<td><strong>Nucleotide RTI</strong></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td></td>
<td>(Note: drug interaction with ddl necessitates dose reduction of latter)</td>
</tr>
</tbody>
</table>
# Dosages of Antiretroviral Drugs for Adults and Adolescents

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<tr>
<td><strong>Non-nucleoside RTIs</strong></td>
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</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>600 mg once daily</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>200 mg once daily for 14 days, then 200 mg twice daily</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Indinavir/ritonavir (IDV/r)</td>
<td>800 mg/100 mg twice daily</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>400 mg/100 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>533 mg/133 mg twice daily when combined with EFV or NVP</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>1250 mg twice daily</td>
</tr>
<tr>
<td>Saquinavir/ritonavir (SQV/r)</td>
<td>1000 mg/100 mg twice daily or 1600 mg/200 mg once daily</td>
</tr>
</tbody>
</table>

**key**
2.9 Non ARV’s Essential commodities for care of PLWHA

- Essential HIV and related testing materials and reagents
- Essential medicines for Opportunistic Infections
- Medicines for pain relief, palliative care, and mental health problems
- Condoms
- Medical supplies: gloves, syringes, needles
MAJOR QUESTIONS IN WHO ART GUIDELINES

- WHEN TO START
- WHEN TO SUBSTITUTE
- WHEN TO SWITCH
- WHEN TO STOP
- SPECIAL SITUATIONS
- WHO GLOBAL RECOMMENDATIONS
- REGIONAL AND COUNTRY CRITERIA
- DRUG FORMULARY
  - 1ST AND 2ND REGIMENS
  - BASIC INFO FOR FORECASTING AND PROCUREMENT
Unit 3
Product Quantification
3.1 Some Key Principles of Quantification

- Try to use two quantification methods to validate your estimations
- Do not forget that initially you will have to constitute a security stock as well as to fill the supply pipe line (lead time!)
- Rate of expansion may be bigger than you expect
Some Key Principles of Quantification (Cont'd)

- Define the units in which quantities are expressed clearly: try to use basic units as tablets, vials or capsules etc
- Calculate/estimate losses/waste
- Use VEN if necessary
- See formula table 4.4 in “Battling HIV/AIDS”
- Drugs to be included need to be defined for each type of health facility whose requirements are being estimated
- Standard treatment protocols need to be there to set the consensus about the appropriate use of these drugs.
3.2 Quantification Methods for HIV/AIDS Drugs

- Consumption (Usage) Method
- Adjusted Consumption (Usage) Method
- Patient Morbidity Standard Treatment Method
Consumption Method

• Based on past consumption records to estimate future needs, adjusted for stock-outs, expiration of overstocked items and projected changes in utilization.

• Cannot be used for rapidly changing or new programs (at this moment ART programs)
Adjusted Consumption Method

- Relies on past consumption records from other facilities or even other countries
- Data is extrapolated and adjusted to local circumstances like population coverage or service level provided
- Can be very useful in start-up situations
Adjusted Consumption Method

• Advantages:
  – Less complicated, easy to calculate
  – Can be very accurate when based on accurate statistics and conformity to treatment guidelines

• Disadvantages:
  – Difficult to adjust for changes in demand and use
  – May perpetuate irrational use of medicines and lab tests
Patient Morbidity Standard Treatment Method

• Based on the number of expected patients \( \times \) the drugs and materials consumed according to the standard treatment protocol

• In new ART programs capacity is often the limiting factor
Patient Morbidity Standard Treatment Method

• Advantages
  – Works well in new programs
  – Encourages conformity to treatment guidelines
  – Prompts periodic evaluation of needs

• Disadvantages
  – Time consuming, more complex
  – Requires reliable and up to date morbidity and patient attendance records
  – Requires sound professional judgment on target treatment population
Conclusions

- The selection process of ARV is subject to frequent reviews as a result of fast changing products and treatment guidelines
- The quantification of ARV will likely be more dependent on the capacity of ART programs and associated funds than on morbidity numbers